- All NDMBs must be monitored from induction of anesthesia to emergence. Loading doses are not affected but maintenance dosing needs monitoring. Decreased potency and duration of aminosteroid NDMBs (rocuronium, vecuronium, and pancuronium) by PK/PD interaction, an increase in hepatic metabolism/biliary excretion, upregulation of acetylcholine receptors, and clearance. No impact on onset of NDMBs. Mivacurium and atracurium not concerned. No association between epileptic status, CMZ, and laudanosine. Faster recovery of neuromuscular block and more rapid speed of infusion with cisatracurium.
- Decreased blood level of midazolam (CTP3A4 induction); reduction of propofol concentration (common metabolic pathway CYP3A4, CYP2C8, and CYP2B6)
- No impact on sufentanil (total clearance > hepatic clearance) and remifentanil (esterase-dependent metabolic pathway not affected by CYP450). Higher dose of fentanyl needed (strongly catalyzed by CYP3A4). Combine objective assessment of analgesia (pupillometry or ANI) to usual hemodynamic variations to improve effective dosage. Morphine can be used without specific modification. CMZ decreases morphine-3-glucuronide-induced enhancement of $Na_v1.7$, and the combination of CMZ-morphine reverses late tactile allodynia in a neuropathic model of pain. No increase of morphine-induced hypercapnia/hypoventilation.
- CMZ decreases bioavailability of paracetamol. Short-term prescription of paracetamol with daily dose <4 g/d; risk of hepatotoxicity among long-term user of paracetamol, <3 g/d in adult. Ibuprofen can displace CMZ protein binding in uremic pt.
- PNB with recommended dose and performed under US is safe in CMZ pts. Lidocaine blocks the residue in the S6 segment of domain IV of Na_v with a lesser interaction with the S4 segment of domains III and IV (voltage sensor). A common site of binding for local anesthetics and CMZ was defined in the S6 segment. Lidocaine and CMZ produces an additive interaction on Na^+ ion passage. CMZ can induce the metabolism of lidocaine (CYP3A4 and CYP1A2 pathway and a high hepatic clearance). Ropivacaine and levobupivacaine are hydrolyzed by CYP1A2 and less by CYP3A4. Beneficial effect of combined oral CMZ and repetitive peripheral nerve block in pts suffering from trigeminal neuralgia. Clinical signs associated with LAST can mimic some signs of a CMZ overdose. In cases of suspected LAST, check blood level of CMZ and LA, initiate basic and advanced life support and pharmacologic measures according guidelines. US required to reduce vascular puncture and to obtain analgesia with a reduced total dose of LA.
- Consider increased tendency to hyponatremia in urologic procedures or neurosurgery (preop use of hyperosmotic solutions)

Postoperative Period

- Keep in mind the possible hemodynamic effects (arrhythmias, arterial hypotension or hypotension, cardiac ischemia).
- Neuromuscular monitoring of NDMB in PACU to confirm complete recovery.
- Resume CMZ after surgery at preop dosage. Use caution when oral alimentation is not rapidly obtained or when hypovolemic status after major surgery. Plasma level of CMZ must be checked after resuming and side effects evaluated.
- Thromboprophylaxis for the postop period according guidelines (cumulative risk of surgery and treatment by CMZ).
- Oral hormonal contraceptives call for additional safety precautions.
- Watch for natremia in the postop period after major and/or urologic interventions, geriatric or noncommunicating pts, and when pts are taking diuretics.
- Arrhythmias and atrioventricular block associated with CMZ remain possible. ECG and blood tests (troponin, BNP) in case of cardiovascular instability or after major surgery in pts receiving beta-blockers, CCBs, antiarrhythmics, or antihypertensives.

Anticipated Problems/Concerns

- PK/PD of CMZ and impact on CYP450 system
- Blood level of CMZ, hyponatremia
- Use caution in geriatric pts (confusion)
- Monitoring of neuromuscular block required (particularly aminosteroid muscle relaxants)
- CV impact and thromboembolism risk
- Antihyperalgesic drug
- Additive interaction between CMZ and lidocaine

Chemotherapeutic Agents

Juan P. Cata | Marc A. Rozner

Risk

- Cancer is the second most common cause of death in USA. In 2016, about 1,685,210 pts will be diagnosed with cancer and 595,690 will die of it.
- More than two-thirds of all cancers are diagnosed in people 50 y of age or older. Prostate cancer is the most common among men, while breast cancer is the most frequent in women. In both genders, lung cancer is the leading cause of death due to cancer.

Uses

- Drugs or biological agents (interleukins and interferon) are commonly used to (1) stop cancer cells from proliferating, migrating, and invading and/or (2) facilitate their recognition by the immune system.
- Traditional chemotherapy agents, targeted chemotherapies, and immunotherapies are still front-line drugs for the treatment of solid and hematologic malignancies.
- Neoadjuvant (before surgery) chemotherapy (and possibly radiation) remains the treatment of choice for many solid cancers.

Perioperative Risks

- Intraop bleeding due to thrombocytopenia, postop infection, complications (leukopenias), blood transfusions (anemia).
- Cardiac insufficiency and fluid overload (due to cardiotoxic agents such as the anthracyclines). Pulm toxicities can lead to periop pulm edema.
- Acute kidney injury (nephrotoxic agents).
- Mononeuropathy (neurotoxic drugs). Bone demineralization (osteopenia) is a risk for fracture after inadequate pt positioning.

Classification According to Mechanism of Action

Class	Activity	Agents
Alkylating agents	Covalent binding to nucleic acids or proteins	Nitrogen mustards (cyclophosphamide, melphalan, chlorambucil) Aziridines (thiotepa and mitomycin C) Procarbazine, oxazaphosphorines (cyclophosphamide, ifosfamide) Alkyl alkane sulfonates (busulphan) Nitrosoureas (carmustine, bendamustine, lomustine) Tetrazines (dacarbazine, mitozolomide, temozolomide)
Antimetabolites	Competition with natural substrates for the active site	Pyrimidine analogues (fluorouracil, cytarabine, sapacitabine, gemcitabine) Purine analogues (6-mercaptopurine, thioguanine) Folic acid antagonists (methotrexate)
Spindle agents	(1) Vinca alkaloids: Binding to microtubules (assembly inhibition) (2) Taxanes: Binding to microtubules (assembly facilitation)	Vincristine, vinblastine Paclitaxel, docetaxel, abraxane Epothilones, discodermolide
Antibiotics	Alteration of function and synthesis of nucleic acids	Anthracyclines (derived from *Streptomyces*), most commonly doxorubicin, daunorubicin, and epirubicin (most generic names except mitoxantrone end with -rubicin), actinomycin D, bleomycin, mitomycin C, vosaroxin
Heavy metals	Platinum agents: Crosslink with DNA strands—inhibition of protein synthesis	Cisplatin, carboplatin, oxaliplatin
Topoisomerase inhibitors	Inhibition of DNA replication	Topoisomerase I inhibitors: Camptothecin, irinotecan, topotecan Topoisomerase II inhibitors: Epipodophyllotoxin derivatives, vosaroxin
Hormone receptors, antagonists, and hormonal agents	(1) Estrogen receptor antagonists (2) Aromatase inhibitors (block conversion of androgens to estrogens) (3) Androgen receptor antagonists (4) Gn-RH antagonist (5) LHRH agonists	(1) Tamoxifen (2) Anastrozole, letrozole, exemestane (3) Enzalutamide (4) Degarelix
Proteasome inhibitors		Bortezomib
Monoclonal antibodies and small-molecule inhibitors	Direct effects against receptors or signaling molecules	Anti-HER-2 antibody (trastuzumab), antiangiogenesis (bevacizumab, ramucirumab), anti-EFGR antibody (cetuximab), anti-bcr-abl antibody, anti-CD20 antibody (rituximab), anti-CD30 antibody (brentuximab), and anti-CD33 antibody (SGN-33, AMG-330) Tyrosine kinase inhibitors (gefitinib, erlotinib), PIK-1 inhibitors (volasertib), FLT3 inhibitor (sorafenib, midostaurin, quizartinib), JAK inhibitors (pacritinib), mTOR inhibitors (everolimus), aurora A kinase inhibitor (alisertib)
Histone deacetylase inhibitors CDK4-CDK6 inhibitors	(1) Selective of paninhibition of HDAC (2) Inhibition of DNA synthetic phase	Vorinostat, romidepsin, belinostat, mocetinostat, panobinostat Palbociclib, ribociclib, abemaciclib
Biological response modifiers		Interferon, interleukin 2 Anti-PD-1 antibodies (nivolumab, atezolizumab, pembrolizumab, pembrolizumab) CTLA-4 blocker (ipilimumab) Thalidomide, lenalidomide

Key References: Ai D, Banchs J, Owusu-Agyemang P, et al.: Chemotherapy-induced cardiovascular toxicity: beyond anthracyclines, *Minerva Anestesiol* 80(5):586–594, 2014; Sahai SK: Perioperative assessment of the cancer patient, *Best Pract Res Clin Anaesthesiol* 27(4):465–480, 2013.

Perioperative Implications

Preoperative Considerations

- Hematologic toxicities (anemia, neutropenia, and/or thrombocytopenia) are among the most common toxicities caused by chemotherapeutic agents. Mythramycin can cause significant bleeding disorders (thrombocytopenia plus depletion of factors II, V, VII, and X). Preop complete blood count is recommended to address the severity of anemia and thrombocytopenia. PT/INR and APTT should be indicated for pts who have received mythramycin before surgery. The administration of blood products is usually necessary in symptomatic pts and those at risk for spontaneous bleeding (<10,000 platelets/dL) or if regional anesthesia is being considered.
- Cardiovascular toxicities: Arterial Htn (ponatinib and VEGF inhibitors), pulm arterial Htn (dasatinib), CHF, acute vascular occlusive events (nilotinib), and increased risk of CAD and sudden death. QTc prolongation has been reported after the administration of targeted agents; therefore ECG is recommended in pts treated with drugs. Echocardiographic evaluation of pts who have been treated with anthracycline agents is recommended before and after treatment and unrelated to the need for surgery. B-type naturetic peptide measurement might be an adequate substitute (with omission of echocardiography with BNP <100 pg/mL) in an asymptomatic pt, although this issue has not been settled. Fluorouracil can cause coronary artery vasospasm during administration with symptoms, but whether or not these events represent true underlying CAD still remains in question. Nevertheless, a pt with a history of chest discomfort during 5FU administration should be evaluated by a cardiologist.
- Pulmonary toxicities such as unilateral or bilateral pleural effusions or parenchymal infiltrates are not unusual. Chest x-ray and drainage of effusions might be needed in symptomatic pts. Although supplemental oxygen therapy and possibly fluid administration can worsen the pulm toxicity associated with bleomycin, hypoxemia can be observed in pts treated with monoclonal antibodies, TKIs, and IL-2.
- Nephrotoxicities manifesting as mild proteinuria, nephrotic syndrome, interstitial nephritis, profound hypomagnesemia, and renal failure have been reported after drugs such as cisplatin (or any platin) and antivascular endothelial growth factors. Preop serum Cr concentrations and calculation of the GFR rate are necessary to identify the acute onset or worsening of chronic renal failure, which might require treatment before surgery.
- Electrolyte abnormalities and fluid retention usually manifest as fatigue, ECG abnormalities, wt gain, periorbital edema, and lower limb edema. Vincristine, vinblastine, melphalan, cyclophosphamide, cisplatin, and immunomodulator drugs (IL-2 and levamisole) can cause hyponatremia. All of the platins can induce a magnesium-wasting nephrotoxicity, although some reports categorize the risk to be cisplatin > carboplatin > oxaliplatin. Preop serum electrolyte determination and ECG evaluation might be indicated in symptomatic pts. Pleural or pericardial effusions and cerebral edema can be observed after treatment with TKIs. Echocardiographic evaluation and chest x-rays might be recommended to evaluate the magnitude and direct treatment of pts with symptomatic or large effusions. Tumor lysis syndrome (hyperkalemia, hyperphosphatemia, and metabolic acidosis) in pts with hematologic malignancies requiring surgery needs careful evaluation of the pt's hydration status and electrolyte imbalances.
- Gastrointestinal adverse events including nausea, vomiting, diarrhea, GER, and abdominal pain are commonly reported. Pancreatitis and elevation of liver enzymes should be considered in pts treated with targeted agents. Assessment of the severity of the GER is needed to initiate preop treatment with proton pump inhibitors or anti-H_2 histaminic drugs. In pts with liver transaminitis, the use of acetaminophen should be avoided.
- Neurologic toxicities include peripheral neuropathy (sensorineural and/or motor) and autonomic

dysfunction, especially after platin, vincristine, or vinblastine use. Posterior reversible leukoencephalopathy and stroke have been reported in pts treated with antiangiogenic agents. Cognitive impairment is commonly reported in women treated with tamoxifen.
- Endocrine adverse events, such as hyperglycemia in pts taking dexamethasone and abnormal thyroid function in those treated with targeted therapies, have been reported.
- Musculoskeletal symptoms include cramps, myalgia, bone pain, and arthralgias.
- Ophthalmologic complications such as blepharitis, keratitis, xerophthalmia, and corneal ulcerations have been reported in pts treated with targeted therapies. Nasolacrimal tear duct obstruction has been reported after paclitaxel, radioactive iodine administration, and external beam radiation to the head/neck area causing profound xerophthalmia.
- Dermatologic adverse events can range from mild skin rashes to panniculitis and Stevens-Johnsons syndrome. They can also result from graft-versus-host disease in pts who have undergone stem cell or bone marrow transplants. Mucositis and stomatitis are frequent with most chemotherapeutic agents as well as radiation to the head and neck. Wound healing can be affected after the use of bevacizumab.

Vascular Access
- Vascular fragility, venous sclerosing, and poor venous access are commonly seen in pts who have received multiple regimens of chemotherapy. The need for a peripheral inserted central venous catheter should be considered in the preop visit. Occasionally, preanesthesia placement of a central venous cath is required.

Airway
- Difficult ventilation or endotracheal intubation should be considered in pts receiving corticosteroids or who have undergone radiation to the head and neck. Pts with oral mucositis and thrombocytopenia are at risk for airway trauma and bleeding. Pts with ocular toxicities might be at risk for eye injuries during airway instrumentation.

Induction (General Anesthesia)
- Rapid sequence induction might be needed in pts with moderate to severe GER. Hyperkalemia should be considered in pts with renal failure or tumor lysis syndrome in whom rapid sequence induction is indicated. Careful titration of hypnotics such as propofol is recommended in pts who have received cardiotoxic agents. Pts with autonomic dysfunction (due to taxanes) can develop significant arterial hypotension during induction of general anesthesia. Prolonged muscle relaxation after succinylcholine can be seen in pts treated with cyclophosphamide (inhibition of pseudocholinesterase). Dehydration should be considered in pts with protracted vomiting and diarrhea; therefore intravascular volume replacement and careful induction of general anesthesia is warranted in these pts.

Maintenance (General Anesthesia)
- Careful titration of anesthetic agents, analgesics, and muscle relaxants is recommended in pts treated with procarbazine, thalidomide, and muscle-wasting chemotherapies such as vincristine. Pulm edema can occur after aggressive fluid resuscitation in pts treated with agents such as IL-2, cardiotoxic drugs, or bleomycin and can complicate assessment and replacement of the intravascular volume where indicated in pts treated with nephrotoxic agents.

Positioning
- Careful positioning should be considered in pts with mononeuropathies or polyneuropathies, alopecias, skin bruises, blisters, and osteopenias. Pts with ocular toxicities need proper care of the eye to diminish the risk of corneal abrasions.

Regional Anesthesia
- Thrombocytopenia (due to myelosuppressive drugs), coagulopathy (associated with Mythramycin), and the presence of mononeuropathy or polyneuropathy might contraindicate the use of regional anesthesia.

Postoperative Period
- NSAIDs and acetaminophen should be used carefully in pts treated with nephrotoxic (cisplatin) and hepatotoxic (mithramycin, L-asparaginase) agents and targeted therapies. Cognitive impairment should be taken into consideration in pts treated with tamoxifen.
- Monitoring of hemodynamics and fluid status can be complicated in pts who have received anthracyclines and targeted chemotherapeutic agents that can possibly induce myocardial dysfunction, especially under high workload stress, which cannot be predicted by coronary artery evaluation (such as an adenosine-nuclear perfusion test) where coronary workload reserve has been compromised but coronary anatomy remains intact. Drugs that affect alveolar vascular permeability (such as bleomycin) can also complicate postop hemodynamic management, especially in the face of profound periop blood loss with resuscitation.

Hyperthermic Intraoperative Chemotherapy
- Complex surgical procedure involving extensive peritoneal stripping, tumor debulking, multiple visceral resections, and the delivery of high-dose hyperthermic chemotherapy to the abdominal cavity. Adequate fluid resuscitation is needed, particularly when cisplatin (risk of nephrotoxicity) is used. The need for fluid status monitoring can persist well into the postoperative period.

Cilostazol

C. David Mazer | Niamh McAuliffe

Uses
- Phosphodiesterase inhibitor with antiplatelet aggregation and arteriolar vasodilator properties.
- Prescribed for intermittent claudication in pts with peripheral arterial disease.
- Lowers restenosis rates after peripheral endovascular procedures in Asian populations.
- Secondary prevention of cerebral infarction with less hemorrhagic conversion than aspirin in Asian populations.
- Use has been limited by tolerability due to high incidence of side effects.

Perioperative Risks
- Plt dysfunction
- Unknown effect on periop blood loss
- Drug interactions
- Tachycardia

Overview/Pharmacology
- 6-[4-(1-cyclohexyl-1*H*-tetrazol-5-yl) butoxy]-3,4-dihydro-2(1*H*)-quinolinone
- Pharmacodynamics:
  - Antiplatelet effect: Strong and specific reversible inhibitor of PDEIII, which increases cAMP in plts, smooth muscle, myocytes, and adipose tissue. This decreases thromboxane A2 production and inhibits plt, aggregation.
  - Reversible plt, inhibition, with duration of up to 12 h. Recovery of plt function 48–96 h after drug cessation with no rebound increase in plt aggregation.
  - Vasodilatation: It targets PDE3 in smooth muscle cells resulting in vessel relaxation.
  - Antiproliferative effect: Increased cAMP upregulates antioncogenes P53 and P21 and hepatocyte growth factor, which induces apoptosis in vascular smooth muscle and inhibits smooth muscle proliferation in vascular beds.
  - Anti atherosclerotic: Alters monocyte chemoattractant protein-1, which recruits monocytes to atherosclerotic lesions.
- Pharmacokinetics:
  - Absorption: Dose—100 mg twice daily to reduce stent restenosis in cardiac patients. Oral administration with peak plasma concentration at 2 h. Steady state is achieved within 4 d. Dietary fat increases absorption and max concentration with potential toxic effects, therefore administer 30 min before or 2 h after meals.
  - Distribution: Cilostazol is 95–98% protein-bound, predominantly to albumin.
  - Metabolism: Hepatic metabolism by cytochrome p450 pathway giving rise to potential drug interactions. Hepatic metabolism involves CYP3A4 (major), CYP1A2 (minor), CYP2C19 (major), and CYP2D6 (minor). There are two major metabolites, the dehydrometabolite is 4–7 times as active as a plt inhibitor and the 4′-trans-hydroxy metabolite is one fifth as active.
  - Excretion: Excretion is predominantly renal, with 74% of metabolites in urine. The elimination half-life is 11–13 h.
- Clinical:
  - Peripheral arterial disease: Approved by the USA FDA for treatment of intermittent claudication because of the drug's ability to decrease plt function and increase vasodilation. Modest improvement in initial claudication distance as compared with placebo (31.41 meters, 95% CI 22.38–40.45 meters). Indicated when lifestyle changes and other therapies have not provided adequate benefit. No evidence of mortality benefit. Has been shown to reduce restenosis and reocclusion rates after peripheral endovascular procedures. May result in lower in-stent stenosis rates after carotid artery stenting.
  - Cerebrovascular disease: Shown to be noninferior to aspirin in secondary stroke prevention in a large RCT in an Asian population, with fewer bleeding events compared with aspirin. May have a role in prevention of intracranial arterial stenosis.
  - Cardiac disease: No reduction in MACE or mortality. Has been associated with a reduction in in-stent restenosis after coronary stent placement in some pt populations. No significant increase in bleeding noted; however, caution advised when used with aspirin or clopidogrel. Genetic polymorphisms in CYP2C19 reduce effectiveness of clopidogrel; this does not seem to be the case with cilostazol, making it a potential option in cases of "clopidogrel resistance." Cilostazol is contraindicated in pts with CHF because of its mechanism of action as a phosphodiesterase enzyme III inhibitor; also contraindicated in pts with moderate to severe renal or hepatic dysfunction. Contraindicated in pts with